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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/695,509	SCHWARTZ ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-22,24,26-29,31 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-22, 24, 26-29, 31 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 3/31/2009 in response to the previous Non-Final Office Action (10/01/2008) is acknowledged and has been entered.

Claims 20-22, 24, 26-29, 31 and 33 are currently pending and under consideration.

Rejections Maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20, 22, 24, 26-17, 29, 31 and 33 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. However, the rejection has been modified in view of Applicants amendments.

In the present case, the claims recite "administering to a patient a composition comprising an effective amount of 25-hydroxyvitmain D or an alkylated, glycosylated, arylated, halogenated, hydroxylated or orthoesterified analog, salt, or derivative thereof…, wherein said effective amount being an amount which increases serum levels of 25-hydroxyvitamin D or its analog, salt or derivative thereof to between 20 and 250 nmol/L. Applicants assert that an ordinary skilled practitioner could readily quantitate this amount. For example, Applicants submit that, as far back as 1977, studies were published which correlated serum levels of 25 (OH)D to the amount administered (see, e.g., Stamp et al. Lancet 1977 1: 1341-1343.). Thus, while the Examiner acknowledges that an effective amount of 25-hydroxyvitamin D could readily be quantitated by one of ordinary skill in the art. The Examiner recognizes that the claims are not solely limited to 25 hydroxyvitamin D, but encompass alkylated, glycosylated, arylated, halogenated, hydroxylated or orthoesterified analog, salts or derivatives of. As such, one of skill in the art would not be apprised of the scope of the invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20, 22, 24, 26-27, 29, 31 and 33 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the prior office action. Note: The rejection has been maintained, but amended in view of Applicants amendments.

In the instant case, the claims recite a method for inhibiting tumor cells, ... comprising the step of administering to a patient a composition comprising an effective amount of 25-hydroxyvitamin D, or or an alkylated, glycosylated, arylated, halogenated, hydroxylated or orthoesterified analog, salt or derivative thereof capable of being hydroxylated by vitamin D 1-alpha hydroxylase in a target organ ... Thus, the claims broadly encompass a genus of derivates of 25-hydroxyvitamin D or an alkylated, glycosylated, arylated, halogenated, hydroxylated or orthoesterified analog thereof which are hydroxylated in the 1 position by 1-alpha hydroxylase resulting in intra-target organ levels of 1,25-dihydroxyvitamin D. However, the written description in this case only sets forth 25-hydroxyvitamin D which is converted to 1,25-dihydroxyvitamin D by 1-alpha hydroxylase thereby resulting in intra-target organ cell levels of said 1,25-dihydroxyvitamin D.

In response to the previous rejection, Applicants assert that the claims have been amended to provide a representative number of species, namely, the alkylated, glycosylated, arylated, halogenated, hydroxylated or orthoesterified" analogs, salts or derivatives of 25(OH)D, which are related to 25(OH)D in structure and function. Moreover, Applicants contend that the specified analogs, salts, or derivatives are capable of being hydroxylated by a specific enzyme (vitamin 1-alpha hydroxylase) in a target organ. Thus, Applicants assert that this functionality is coupled with the known or disclosed correlation between structure and function and is believed to sufficiently show that Applicant was in possession of the claimed genus.

These arguments have been carefully considered, but are not found persuasive.

In the present, the Examiner acknowledges Applicants arguments and amendments and appreciates the amendment to incorporate alkylated, glycosylated, arylated, halogenated, hydroxylated or orthoesterified" analogs of 25 (OH)D into the claims. However, the Examiner recognizes that the claims now encompass an even greater amount of compounds since the derivatives are derivatives of alkylated, glycosylated, arylated, halogenated, hydroxylated or orthoesterified" analogs of 25 (OH)D, as well as 25 (OH)D. Yet, the specification appears to be silent on how far away one of skill in the art may deviate from an alkylated, glycosylated, arylated, halogenated, hydroxylated or orthoesterified" analog of 25 (OH)D or 25 (OH)D. Moreover, the specification appears to be silent on any other analog or derivative of 25-hydroxyvitamin D which can be converted to 1,25-dihydroxyvitamin D. Therefore, the rejection is maintained.

Claims 20-22, 24, 26-29, 31 and 33 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

Claims 20-22, 24, 26-29, 31 and 33 are drawn to a method of inhibiting tumor cells comprising administering an effective amount of 25-hydroxyvitamin D or an analog, salt or derivative thereof. As such, the invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of inhibiting tumors cells, while reducing the risk of UV radiation exposure or vitamin D toxicity, said tumor cells being prostate cancer cells, breast cancer cells, skin cancer cells, pancreatic cancer cells, colon cancer cells, pancreastic cancer cells or lung cancer cells, said method comprising administering to a patient an effective amount of 25-hydroxyvitamin D or an analog, salt, or derivative thereof capable of being hydroxylated by vitamin D 1-alpha hydroxylase in a target organ to increase levels of a metabolite of said 25-hydroxyvitamin D or its said analog, salt or derivative in said tumor cells in a target organ wherein the tumor cells have a hydroxylase enzyme for synthesizing 1,25-dihydroxyvitamin D from said 25-hydroxyvitamin D and results in intra-target organ cell levels of said 1,25-dihydroxyvitamin D between 25 and about 250 nmol/L. Thus, the breadth of the claims appear to suggest that the administration of an effective amount of a 25-hydroxyvitamin D or an analog, salt, or derivative thereof capable of being hydroxylated by vitamin D 1-alpha hydroxylase in a target organ to increase levels of a metabolite of said 25-hydroxyvitamin D or its said analog, salt or derivative in said tumor cells in a target organ, wherein the tumor cells have a hydroxylase enzyme for synthesizing 1,25-dihydroxyvitamin D from said 25-hydroxyvitamin D and results in intra-target organ cell levels of said 1,25-dihydroxyvitamin D between 25 and about 250 nmol/L is effective for the inhibition of tumor cell growth. In other words, the breadth of the claims appears to suggest that the increased level of the metabolite and not the compound administered has the inhibiting effect.

Guidance in the specification and Working Examples

The specification teaches that one aspect of the invention comprises increasing the local cellular levels of $1,25(OH)_2D$ by administering an effective amount of a Vitamin D metabolite which can be metabolically converted by the target cells to $1,25(OH)_2D$ for the prevention or treatment of cell proliferation, invasiveness, or metastasis (page 17, lines 10-15). With regards to the effective amount, the specification teaches that an effective amount of 25 (OH)D administered into the target organ would be any amount which, when administered, increases local cellular levels of 25(OH)D, but maintains serum levels of 25(OH)D within this "normal" range, wherein normal range is a concentration of 25OHD in serum about 20-150 nmol/L (page 18, lines 1-14). Alternatively, the

specification teaches that an alternative determination of an effective amount of 25(OH)D administered in accordance with the method of the subject invention is to administer an amount which raises the level of 25(OH)D toward the high end of its normal range in the target organ, but which does not raise systemic 1,25(OH2)D above the high end of its normal range, wherein the normal serum levels of 1,25 (OH2)D range between about 38-144pmol/L (Page 18, lines 15-24). For example, the speciation teaches that the subject method of administering a metabolic precursor of $1,25(OH)_2D$ to a patient has been shown to be successful in producing $1,25(OH)_2D$ by prostatic cancer cells and two primary culture of cells, NP96-5 and BPH96-11 (page 19, lines 21+). Moreover, the specification teaches that colon or breast cells have also been shown to possess 1 - OHase activity (page 25, lines 1-2). The specification further teaches that in one embodiment, a polynucleotide construct containing a gene that codes for 1a-OHase can be used to treat a cell exhibiting benign prostatic hyperplasia. Thus, while the specification contemplates what the effective amount of 25-hydroxyvitamin D should be within the target organ relative to normal concentrations and dangerous concentrations, the specification appears to be silent on a correlation between the "amount" of 25-hydroxyvitamin D" needed to increase 1,25-dihydroxyvitamin D in the target cell and inhibition of tumor growth. In other words, the specification appears to be concerned with administering an amount of 25-hydroxyvitamin D within the normal range, but is silent on the conversion of 25-hydroxyvitmain D to 1,25-hydroxyvitamin D in the target cell and the result being effective at inhibiting tumor growth. Similarly, while the specification teaches that prostatic cancer cells and two primary culture of cells, NP96-5 and BPH96-11 successfully produce 1,25 dihydroxyvitamin D from 25-hydroxyvitamin D, the specification appears to be silent on the inhibition of the in vitro cells or whether such as conversion is feasable in vivo and have the desired effect, e.g, inhibition of tumor growth. Lastly, as noted above, while the specification provides a number of examples of converting 25-hydroxyvitamin D to 1, 25-dihydroxyvitamin D, the specification appears to be silent on any other analog or derivative of 25-hydroxyvitamin D and the resulting metabolite produced being effective at inhibiting tumor growth.

Quantity of experimentation

The quantity of experimentation in the areas of cancer therapy is extremely large given the unpredictability associated with treating cancer in general and the lack of correlation of in vitro

findings to in vivo success, and the fact that no known cure or preventive regimen is currently available for cancer.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that vitamin D3 undergoes hydroxylation first in the liver to form 25-hydroxyvitamin D3 which is further hydroxylated in the kidney by Vitamin D 1a-hydroxylse to create the biologically active form 1,25 $(OH)_2$D3 (Ma et al. Molecular and Cellualr Endocrinology 2004; 221: 67-74, of record). With regards to 1,25 $(OH)_2$D3, Ma et al. teach that 1,25 $(OH)_2$D3 has been shown to inhibit established prostatic cancer cell lines as well as primary culture of normal and malignant prostatic epithelial cells (page 67, 2nd column last paragraph to page 68, 1st column). Despite the anti-tumor activity of 1,25 $(OH)_2$D3, Ma et al. teach that systemic hypercalcemia resulting from excessive circulation of 1,25 $(OH)_2$D3 has limited its therapeutic potential and has led investigators to propose new strategies to harness the anti-tumor activity of 1,25 (OH)2D3 while circumventing hypercalcemic activity. For example, Ma et al. teach that this discovery has raised the possibility of intra-prostatic conversion of 25(OH)D3 to 1,25(OH)2D3 by endogenous 1a(OH)ase, allowing the use of the less hypercalcermic 25(OH)D3 instead of 1,25(OH)2D3 as a therapeutic approach (page 68, 1st column, 2nd paragraph). However, Ma et al. teach that 1a(OH)ase activity in human prostate cancer cells is dramatically reduced in comparison to cells derived from normal of benign prostatic hyperplasia (page 68, 1st column, 2nd paragraph). Similarly, Hsu et al. (Cancer Research 2001; 61: 2852-2856, of record) quantified the levels of endogenous 1a-hydroxylase activity in a series of primary cultures of human prostatic epithelial cells derived from normal tissue, BPH, adenocarcinomas and several prostatic CA cell lines (page 2852, 2nd column, 3rd paragraph). Specifically, Hsu et al. found that CA cells had approximately 10 to 20 fold lower levels of 1 a-hydroxylase activity compared with cells from normal tissues (page 2852, 2nd column, 3rd paragraph). Likewise, Whitlatch et al. (J. Steroid Biochem. Molecular Biology 2002; 81: 135-140, of record) compared the levels of 1a-OHase activity in prostate cancer cell lines, LNCaP, DU145 and PC-3 and in primary cultures of normal, cancerous and benign prostatic hyperplasia (BPH) prostate cells (abstract). In particular, Whitlatch et al. observed that compared to primary cultures of normal prostate cells, primary cultures of prostate cancer cells and prostate cancer cell lines demonstrate a marked decline in 1a-OHase activity (page

138, 2nd column, last paragraph and page 137, Figure 1). As such, both Hsu et al. and Ma et al teach that the proposed strategy of using 25(OH)D3 as a therapeutic agent for prostate cancer will be ineffective (abstract or Hsu et al. and page 68, 1st column, 1st full paragraph of Ma et al.)

With regards to the unpredictability in the art, those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4, of record) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320, of record) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. In addition, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot

duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Moreover, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042, of record) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation in vitro results to in vivo success, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

In response to this rejection, Applicants contend that the enablement rejection appears to be predicated on the recitation in the claims (prior to the current amendments) of (a) the applicants' general claim to "any" amount of prodrug (metabolic precursor) administered, and (b) the applicants'general claim to "any"analog, salt, or prodrug of 25(OH)D. Thus, Applicants believe that the current claims, as amended, remove these "overbroad" aspects of the invention and provide claims which are enabled by the specification because they clearly teach a person of ordinary skill in the art to carry out the subject method without requireing experimentation that may be "undue". For example, Applicants submit that the 1977 publication by Stamp et al. (Lancet 1977; 1: 1341-1343, copy attached) teaches a correlation of serum levels of 25 (OH)D to the amount administered. As such, Applicants contend that the levels of 25-OHD that need to be administered to achieve serum levels of 25-OHD were clearly known to practitioners of ordinary skill in the art and are believed to be clearly enabled to perform the invention without undue experimentation. Moreover, Applicants assert that the operability of the invention is established, as the Office action points our

in the reference to Ma et al., Hsu et al. and Whitlach et al,. publications, the presence of the 1-alpha hydroxylase enzyme in the target cells will predictably convert the administered prodrug to teh 1-alpha-hydroxylated metabolite.

These arguments have been carefully considered but are not found persuasive.

In response to Applicants arguments, the Examiner recognizes that the present rejection is predicated on the basis that the specification is not enabling for a method of inhibiting tumor cells in a target organ comprising administering to a patient a composition comprising an effective amount of 25-hydroxyvitamin D or an alkylated, glycosylated, arylated, halogenated, hydroxylated or orthoesterified analog, salt, or derivative thereof capable of being of hydroxylated by vitamin D-1-alpha hydroxylase in the target organ, said effective amount being an amount which increases serum levels of 25-hydroxyvitamin D or its analog, salt, or derivative to between about 20 and 250nol/L. In the present case, the specification appears to be silent on a correlation between serum levels of 25-hydroxyvitamin D or its analog, salt, or derivative to between about 20 and 250nol/L and inhibition of tumor cells. As such, if there is no correlation then the examples do not constitute working examples. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention. The unpredictability in the art with respect to treating cancer has been set forth above. Thus, given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation in vitro results to in vivo success, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written. With respect to Applicants reference to three of the references cited above supporting the predictability of the claimed method, the Examiner acknowledges Applicants assertions. However, the Examiner recognizes that Ma et al., Hsu et al. and Whitlach et al do not appear to support Applicants contention that the presence of the 1-alpha hydroxylase enzyme in the target cells will predictably convert the administered prodrug to the 1-alpha-hydroxylated metabolite. In contrast, the Examiner recognizes that both Hsu et al. and Ma et al teach that the proposed strategy of using 25(OH)D3 as a therapeutic agent for prostate

cancer will be ineffective (abstract of Hsu et al. and page 68, 1st column, 1st full paragraph of Ma et al.). As such, the rejection is maintained.

New Rejections Necessitated by amendment:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-22, 24, 26-29, 31 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: a correlation between the effective amount and the preamble. In the present case, the claims recite a method of inhibiting tumor cells comprising administering an effective amount of 25-OHD or an analog, salt or derivative thereof, wherein the effective amount is an amount which increases serum levels of 25-hydroxyvitamin D or its analog, salt or derivative thereof to between 20 and 250 nm/L. However, it is unclear what the relationship is between the effective amount and inhibition of tumor cells.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Primary Examiner
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